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(54) Title: PROCESS FOR THE PRODUCTION OF SEMI SYNTHETIC STATINS VIA NOVEL INTERMEDIATES

(57) Abstract

A process has been provided to produce semi synthetic statins, as for instance simvastatin with a high yield, from another statin, preferably a naturally occurring statin, as for instance lovastatin. Also a number of novel intermediate compounds, prepared during said process, has been provided.

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PROCESS FOR THE PRODUCTION OF SEMI SYNTHETIC STATINS VIA NOVEL INTERMEDIATES

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a process to prepare semi synthetic statines and to intermediates formed during said process.

It is well known that certain mevalonate derivatives are active as hypercholesterolemic agents, which function by limiting the cholesterol biosynthesis by inhibiting the enzyme HMG-CoA reductase. These mevalonate derivatives are the naturally occurring fungal metabolites lovastatin and compactin. But also semi-synthetic and synthetic analogs thereof are active.

The naturally occurring compounds lovastatin and compactin possess a 2-methylbutyrate side chain in the 8-position of the hexahydronaphtalene ring system. Analogs with a 2,2-dimethylbutyrate moiety in this position, such as simvastatin, appeared to be more effective inhibitors of HMG-CoA reductase.

These compounds can be synthesized from the naturally occurring compounds. In principle there are two possible routes for the introduction of an extra α-methyl group in the 8-acyl side chain which are:

1. direct alkylation of the 2-methylbutyrate side chain,
2. removal of the 2-methylbutyrate side chain and introduction of a 2,2-dimethyl butyrate chain.

The main advantage of the direct alkylation route is the relatively high yields that can be obtained. However, there are several drawbacks. Direct methylation of unprotected lovastatin (U.S. patent 4,582,915) results in a rather impure simvastatin, containing a relatively high amount of unconverted lovastatin and many byproducts. Therefore, protection of the pyranone ring is required. A reduction of the byproducts was achieved by protecting the pyranone ring of lovastatin prior to the

alkylation with t-butyl dimethyl silyl chloride (European patent EP299656). However this is a very expensive protecting group. A less expensive protecting group is boronic acid as disclosed in international patent application WO 95/13283. Nevertheless, this route still suffers from the fact that it is difficult to obtain a complete conversion of the 2-methyl butyrate side chain into the 2,2-dimethyl butyrate side chain. Therefore, an additional purification is necessary. For example base hydrolysis of the remaining lovastatin to triol acid with NaOH or LiOH, in which also part of the simvastatin is hydrolysed, followed by crystallization. Alternatively selective enzymatic hydrolysis of lovastatin (U.S. patent 5,223,415) may be applied. However, these extra purification steps will reduce the yield, and make the process less efficient.

The second route, wherein the 2-methyl butyrate side chain is completely removed and another side chain is added, offers intrinsically a better quality product, as the separation of the hydrolyzed product and the esterified product is much easier to achieve compared to the unreacted starting material and the methylated product.

In US patent 4,293,496 the removal of the 2-methyl butyrate side chain is achieved by base hydrolysis of lovastatin with an alkali metal hydroxide, preferably LiOH. This reaction requires long processing times (50-72 hours while refluxing) or rather stringent conditions (120°C-180°C) if shorter process times are used.

In US patent 4,444,784 the introduction of a new side chain to the hydrolyzed lovastatin is disclosed. It involves several separate steps: relactonization of the mevinic acid, protection of the hydroxy group in the pyranone ring by reaction with t-butyl dimethyl silyl chloride, esterification with 2,2-dimethyl butyric acid and deprotection of the hydroxy group of the pyranone ring. The main disadvantages of this process route are the low yields, and the use of an expensive protecting group, *viz.* t-butyl dimethyl silyl.

A much less expensive protecting group is disclosed in US patent 5,159,104. Instead of the t-butyl dimethyl silyl protection of the OH-group in the pyranone ring, the OH-group was esterified with an acetic anhydride or an acylhalide. However, this process still suffers from a poor yield.

The present invention provides a new, rather inexpensive, crystalline intermediate which can be used in both synthesis routes. In addition a novel, quick and less expensive process for the quantitative removal of the 2-methyl butyryl side chain and addition of another side chain, is disclosed, including novel, crystalline intermediates for the preparation of semi synthetic lovastatin and compactin intermediates. Besides that, a much higher yield for the removal of the side chain of about 95% was obtained compared to the yield of about 65% obtained in a comparable process as described by Askin *et al* in J. Org. Chem. 1991 vol 56, pages 4929-4932. Furthermore, by the application of the process of the present invention for the synthesis of semisynthetic statins, as for instance simvastatin, the use of the carcinogenic methyliodide is avoided, which is required in the direct methylation route.
The process of the present invention comprises a surprisingly selective removal of the 8'(R_3')-side chain, for instance the 2-methyl butyryl side chain in lovastatin, to triol acid intermediate and another alcohol, by reduction with a reducing agent such as $LiAlH_4$ or a Grignard reagent, or to a triol acid intermediate and an amide by reaction with an amine. During this reaction the starting material is quantitatively converted into the triol acid intermediate, which offers excellent possibilities for the introduction of various side chains.

DESCRIPTION OF THE FIGURES

Figure 1: Scheme of the process to prepare semi synthetic statins, depicted as formula I, from a statin , preferably a naturally occurring one, by removal of the 8'-side (R_3') chain including the novel intermediates of formula II and IV, depicted as II', III, IV and II. The figure displays only one of the

possible stereoisomers as example, but should not be regarded as limited thereto.

Figure 2: Scheme of the process to prepare semi synthetic statins, depicted as formula I, by applying direct α-methylation on the ester moiety of a compound of formula II'.

SUMMARY OF THE INVENTION

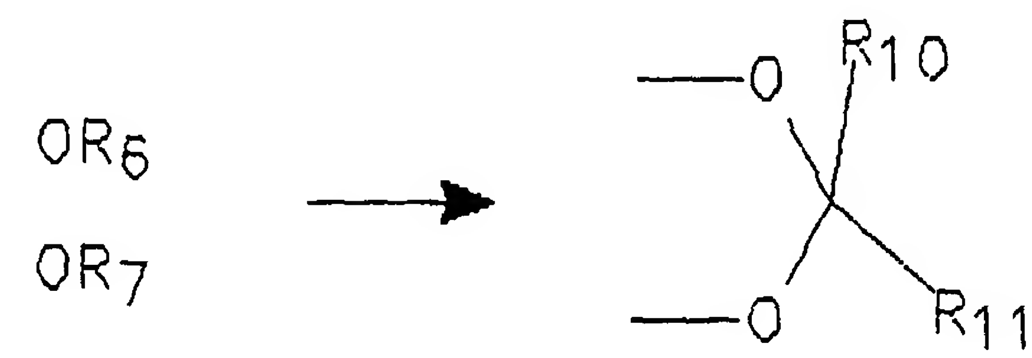
The present invention provides a novel process for the production of semi synthetic statins, defined as formula I, depicted in figure I from a statin defined as formula I, depicted as formula I' in figure I, wherein R_1 and R_2 are independently selected from the group consisting essentially of a hydrogen atom, a hydroxyl, C_{1-10}alkyl, C_{6-14}aryl and C_{6-14}aryl-C_{1-3}alkyl, preferably methyl, and wherein R_3 and R_3' are independently selected from the group comprising R_9-CO- and hydrogen, and wherein R_9 is selected from the group comprising:

(1) C_{1-15} straight or branched alkyl,
(2) C_{3-15}cycloalkyl,
(3) C_{2-15}alkenyl, straight or branched
(4) C_{2-15}alkynyl, straight or branched,
(5) phenyl,
(6) phenylC_{1-6}alkyl-,

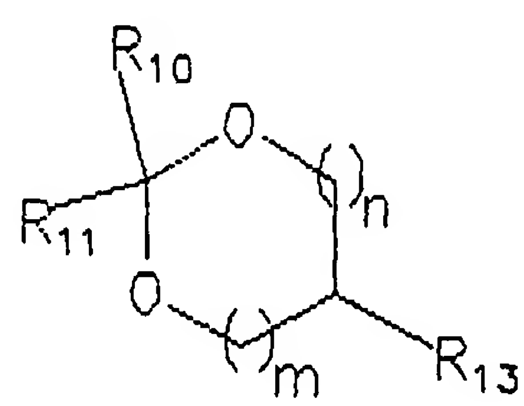
all optionally substituted with one or more of the substituents independently selected from the group comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{6-14}aryl as for instance phenyl or aromatic heterocycle,

preferably R_3 is 2,2-dimethylbutyryl and R_3' is 2-methylbutyryl, and wherein the dotted lines at x, y and z represent possible double bonds, when any are present, being either x and z in combination or x, y or z alone or none, with the proviso that the double bonds of a compound as defined in formula I are the same as the double bonds of a compound as defined in formula I', by ring opening of the lactone by forming an amide bond by reaction with ammonia or with primary amines, preferably n-butylamine and cyclohexylamine or secondary amines, preferably

piperidine and pyrrolidine, and subsequently optional protection of the hydroxyl groups, for instance by formation of a dioxane moiety at R_6 and R_7,



by reaction with a ketone, defined as R_{10}-CO-R_{11}, or an aldehyde defined as R_{10}-CO-H, or an acetal defined as



or $H(CH_2)_nCHR_{13}(CH_2)_m\text{-}OR_{10}CR_{11}O(CH_2)_{m'}CHR_{13}'(CH_2)_{n'}H$

wherein R_{13} and R_{13}' are each independently selected from the groups comprising hydrogen, halogen, C_{1-6}alkyl-, C_{1-6}alkoxy, C_{6-14}aryl as for instance phenyl or aromatic heterocycle and m, n, m' and n' are each independently 0 - 10,

wherein R_{10} and R_{11} are independently selected of the group comprising:

(1) C_{1-15}alkyl, straight or branched,

(2) C_{3-15}cycloalkyl,

(3) C_{2-15}alkenyl, straight or branched,

(4) C_{2-15} alkynyl, straight or branched,

(5) phenyl,

(6) phenylC_{1-6}alkyl-,

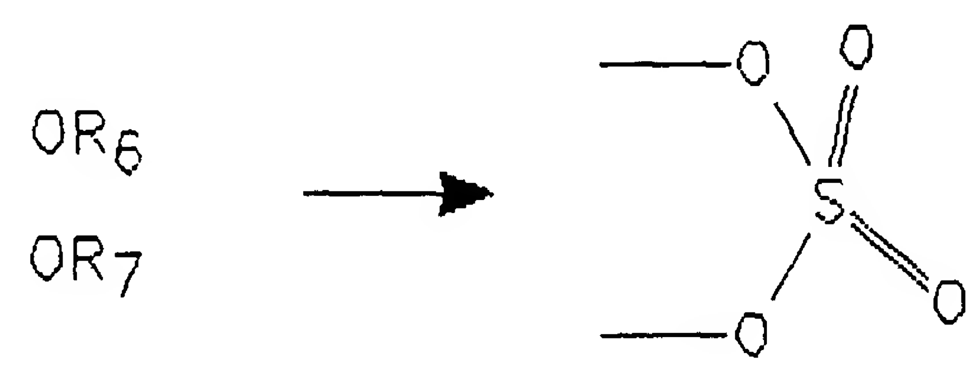
all optionally substituted with one or more of the substituents independently selected from the group comprising halogen, C_{1-6} alkyl, C_{1-6}alkoxy, C_{6-14}aryl as for instance phenyl or an aromatic heterocycle,

(7) hydrogen, with the proviso that R_{10} is not hydrogen,

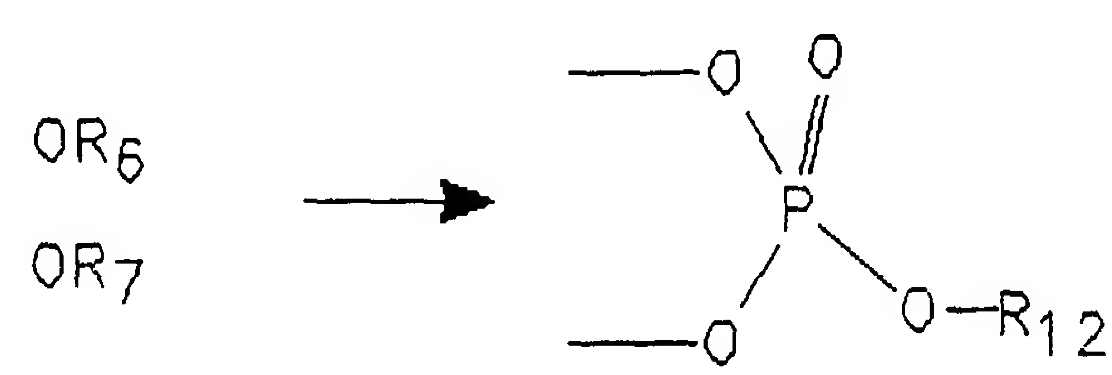
(8) R_{10} and R_{11} are forming an optionally substituted 5, 6, 7 or 8 membered cyclic moiety, in which the substituents comprise halogen and a C_{1-6}alkyl in any combination,

preferably R_{10} and R_{11} are methyl, in the presence of catalytic agents, preferably an acid such as para-toluene sulphonic acid (p-TsOH) or sulfuric acid, or by reaction with silylating agents, preferably t-butyl dimethyl silyl chloride, or by formation of protective groups, such as for instance:

(1) cyclic sulfate,



(2) cyclic phosphate,



in which R_{12} is selected from a group comprising:

(1) C_{1-15} straight or branched alkyl,

(2) C_{3-15}cycloalkyl,

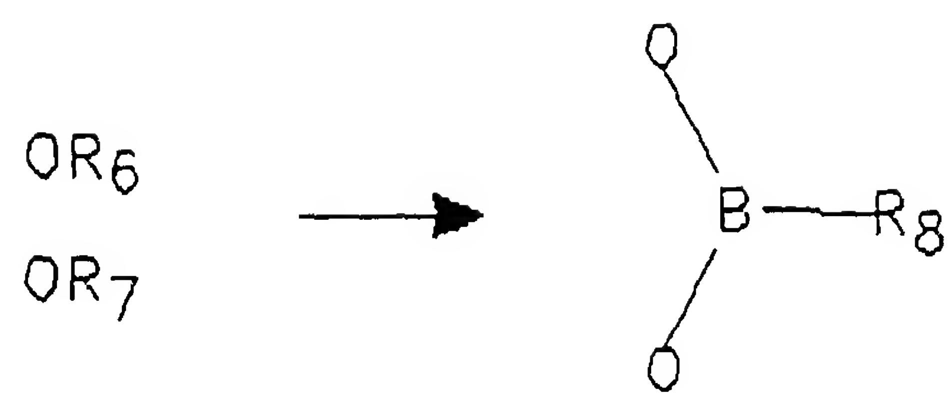
(3) phenyl,

(4) phenyl-C_{1-6}alkyl,

(5) hydrogen,

(6) primary amines, preferably n-butylamine and cyclohexylamine or secondary amines, preferably piperidine and pyrrolidine,

(3) borylidene



in which R_8 is a phenyl optionally substituted by one to five substituents, halogen or C_{1-6}alkyl in any combination, preferably phenyl or para fluoro phenyl,

followed by removal of the ester R_3' moiety by reduction with suitable reducing agents, such as lithiumaluminumhydride, methylmagnesiumchloride or n-butyllithium,

or by reaction with a primary amine R_4NH_2 wherein R_4 is selected from the group comprising

(1) C_{1-15} straight or branched alkyl,

(2) C_{3-15}cycloalkyl,

(3) C_{2-15}alkenyl, straight or branched,

(4) C_{2-15}alkynyl, straight or branched,

(5) phenyl,

(6) phenylC_{1-6}alkyl-,

all optionally substituted with one or more of the substituents independently selected from the group comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy, aryl as for instance phenyl or aromatic heterocycle,

(7) hydrogen,

followed by acylation with the acid chloride or the free acid of the corresponding R_3 group or the optionally symmetric anhydride, with the proviso that in case R_6 and R_7 are hydrogen, the corresponding hydroxyl groups are protected as described above before this acylation reaction is carried out,

followed by the removal of the protective group and of the amide by hydrolysis, into a compound of formula V, depicted in figure I, wherein M forms any pharmaceutically acceptable salt, acid or ester thereof,

optionally followed by lactonization by heating, and finally by crystallization.

The present invention also provides a number of novel intermediates of formula II, depicted as II', III and II in figure I, and of formula IV in figure I, wherein R_1, R_2, R_3 and R_3' and the double bonds x, z and y are defined as above in formula I, and R_4 and R_5 are independently selected from the groups as defined for R_4 in R_4NH_2 above and R_4 and R_5 may form with the nitrogen to which they are attached, a 5, 6 or 7 membered heterocycle moiety such as a pyrrolidine, piperidine or a homopiperidine,

and wherein R_6 and R_7 are independently selected from the group which form:

(1) a dioxane moiety,
with R_{10} and R_{11} defined as above,

(2) a cyclic sulfate,

(3) a cyclic phosphate, with R_{12} defined as above, and with the proviso that when R_3 is hydrogen, R_6 and R_7 may also form a borylidene group, wherein R_8 is defined as above and R_6 and R_7 may be both hydrogen.

The processes disclosed for the preparation of said intermediates above, form a substantial part of the invention. The present invention also provides the preparation of a compound of formula I, as described above, with the proviso that R_3 comprises an alkyl group on the α-position, from a compound of formula I', as described above, with the proviso that R_3' comprises a hydrogen on the α-position, followed by ring opening of the lactone by forming an amide bond by reaction with ammonia or with primary amines, preferably n-butylamine and cyclohexylamine or secondary amines, preferably piperidine and pyrrolidine, and subsequently optional protection of the hydroxyl groups, for instance by formation of a dioxane moiety at R_6 and R_7, with R_{10} and R_{11} defined as above,
followed by direct α-alkylation of the R_3' moiety of formula II, depicted in figure I as formula II', forming a compound of formula II, defined as above, with the proviso that R_3 comprises an alkyl group on the α-position, exemplified in figure II, by

reaction with an alkyl halogenide, for instance methyl iodide (MeI).

This present invention provides the use of the processes as described above for preparing a compound of formula I, as described above, from a compound of formula I', as described above, containing upto about 30% of impurities, as for instance oxidized compounds or di- or tetra-hydro statins. Preferably simvastatin is produced in this way, starting from lovastatin contaminated with dihydrolovastatin and optionally oxidized compounds.

DETAILED DESCRIPTION OF THE INVENTION

The process of the invention comprises the following steps:

1) Conversion of a compound of formula I' defined as above into a compound of formula II' defined as above, by:

a) ring opening of the lactone by formation of an amide bond with an excess of amine optionally mixed with an inert organic solvent as for instance toluene, cyclohexane, tetrahydrofuran, acetonitrile, preferably an amine with a boiling point higher than 60°C, at a temperature above about RT, preferably higher than 60°C, where after complete conversion the excess of amine is removed, for instance by evaporation, or by washing with dilute acid,

b) optionally followed by protecting the hydroxy groups of the former lactone by reaction of the formed amide with a ketone or aldehyde or acetal, optionally mixed with an inert organic solvent as for instance toluene, cyclohexane, tetrahydrofuran, acetonitrile or ethylacetate, between 5°C and 50°C, preferably around room temperature in the presence of a catalytic agent as for instance p-toluene sulphonic acid (p-TsOH) or sulfuric acid,

or by reaction of the formed amide with sulfonyl chloride in dichloromethane at temperatures between -20°C and 20°C, preferably between -5°C and 5°C, followed by oxidation to form the sulfate, for instance with sodiumperiodate in a suitable solvent, for instance a mixture of water and

acetonitrile in the presence of a catalyst, for instance Ruthenium chloride,

or by reaction of the formed amide with phosphonyl chloride in an inert organic solvent as for instance toluene at temperatures between 5°C and 50°C, preferably between 15°C and 25°C, followed by reaction with an alcohol, or an amine or water,

or the formation of borylidene moiety as described in international patent application WO 95/13283 mentioned above,

or the reaction with t-butyl dimethylsilyl chloride as described in US patent US 4,444,784 mentioned above.

2) Conversion of the compound of formula II' formed in step 1 to a compound of formula III as defined above, by removal of the R_3' moiety with a suitable reagent, as for instance:

a) reduction with lithiumaluminiumhydride, aluminiumhydride or diisobutylaluminiumhydride in an inert solvent as for instance toluene or tetrahydrofuran (THF) at temperatures between 0°C and 30°C, preferably between 5°C and 10°C, whereafter the reaction mixture is neutralized with for instance water or potassium hydroxide or sodium hydroxide or ethylacetate to neutralize the excess of lithiumaluminiumhydride,

b) reduction with an organic-metallic compound such as a Grignard reagent in an inert solvent as for instance THF at temperatures between -10°C and 20°C, preferably between -5°C and 10°C, or such as an alkyllithium compound as for instance n-butyllithium in an inert solvent as for instance THF at temperatures between -70°C and -20°C.

c) reaction with a primary amine or ammonia, preferably at a molar ratio equal to or greater than 1:1 with respect to the compound of formula II', optionally in the presence of water or an organic solvent, at a temperature between about 100°C and 250°C, preferably between about 130°C and 200°C, optionally at superatmospheric pressure, dependent on the boiling points of the reactants and solvents applied.

3) Conversion of the compound of formula II as defined above, with the proviso that R_3 is hydrogen (depicted as formula III in Figure I) formed in step 2 to a compound of formula IV in case R_5 is hydrogen, or a compound of formula II in case R_5 is not hydrogen, defined as above by acylation with

a) the corresponding acid chloride in the presence of a base, such as triethylamine as a scavenger for HCl or with

b) the corresponding free acid optionally in the presence of a carbodiimide such as 1,3 dicyclohexylcarbodiimide or

c) the corresponding optionally symmetric anhydride,

in an organic solvent in the presence of a catalyst as for instance 4-dimethylaminopyridine (DMAP) at a temperature between 20°C and 110°C, preferably between 80°C and 110°C.

4) Conversion of a compound of formula II, formed in step 3, to a compound of formula V defined as above, by:

a) removal of the protecting groups at R_6 and R_7 as for instance by hydrolysis in a mixture of water and an organic solvent, such as THF in the presence of a catalyst, as for instance hydrogen chloride or sulphuric acid or p-TsOH at temperatures between 20°C and 100°C, preferably between 30°C and 70°C,

b) followed by the removal of the amide by hydrolysis as for instance in a mixture of a solution of sodium hydroxide or potassium hydroxide in water and an organic solvent as for instance methanol, ethanol, toluene or tetrahydrofuran,

c) optionally followed by reacting with an agent to form a compound of formula V, preferably with a base corresponding to a pharmaceutically acceptable salt, in an organic solvent as for instance methanol, toluene or ethylacetate to form the corresponding salt, for instance the ammonium salt.

5) Conversion of the compound of formula V, formed in step 4, into a compound of formula I, defined as above, by lactonization of the compound V in an inert solvent, as for instance toluene, ethyl acetate or cyclohexane at temperatures between 60°C and 110°C, preferably between 80°C and 100°C. Finally the formed

compound of formula I is isolated by crystallization methods known in the art.

It should be noted that using an amine for the removal of the R_3'-moiety as described in reaction step 2c of the process of the invention offers the possibility to combine the amide formation of reaction step 1a with 2c, whereby a compound of formula I, depicted as I' in figure 1 is directly converted into a compound of formula III, with R_6 and R_7 are each hydrogen.

It should further be noted that the process and compound provided by the present invention are not limited to the stereo isomers depicted in figure 1.

By an aryl group is meant an aromatic hydrocarbon group as for instance phenyl, naphthyl, anthryl or an aromatic heterocycle comprising for instance a nitrogen, a sulfur or oxygen atom.

By a corresponding amine is meant an amine, defined as R_4R_5NH, with R_4 and R_5 defined as above, reacting with a compound of formula I', defined as above, resulting in a compound of formula II', defined as above, wherein R_6 and R_7 are hydrogen and an R_4R_5NCO amide bond is formed, wherein R_4 and R_5 are the same as in the amine used.

By a corresponding acylation agent is meant a compound of formula R_3P, with P is OH or Cl or an anhydride R_3O-CO-O-R_{14}, with R_3 is defined as above with the proviso that R_3 is not hydrogen and R_{14} is defined as R_3, optionally R_{14} is the same as R_3 resulting in a symmetric anhydride, which upon reaction with a compound of formula III, defined as above, results in a compound of formula IV, defined as above, or a compound of formula II, defined as above, wherein R_3 is the same as in the acylation agent used.

In all processes of the present invention the possible double bonds x, y and z of the starting compounds are the same as those in the endproducts. Furthermore, also all other parameters as R groups remain the same for the endproduct compared to the starting material, unless otherwise indicated.

Surprisingly it was found that in the process for preparing pure simvastatin from lovastatin, impure lovastatin may be used,

which may contain upto about 30% of impurities, such as dihydrolovastatin or oxidized lovastatin.

Examples

Experimental

The HPLC-analyses were carried out according to A. Houck et al, Talanta Vol 40 (4), 491-494 (1993): Liquid Chromatopraphic determination of the known low level impurities in lovastatin bulk drug: an application of high-low chromatography

HPLC

-Alliance Waters pomp/injector
-M996 diode array Waters
-Millennium data system Waters

-column: Prodigy 5 C8 250x4.6 mm (phenomenex)

Conditions:

injection volume: 10μl
gradient flow profile (lineair)
A = acetonitrile
B = 0.1% H_3PO_4

TIME min	FLOW ml/min	%A	%B
0	1.5	60	40
1	1.5	60	40
5	1.5	80	20
8	1.5	90	10
16	1.5	90	10
20	1.5	60	40

columntemperature 30°C
Detection at 200 nm and 237 nm.
The samples were mixed in acetonitrile with a concentration of 1.5 mg/ml.

Retention times:
dihydro simvastatin 8.10 min (200 nm)

simvastatin acid	5.77 min (237 nm)
lovastatin	6.34
simvastatin	7.11
dehydro simvastatin	8.90
dimer simvastatin	15.36

Example 1:

Formation of lovastatin piperidinamide:

A mixture of 1 g (2.5 mmol) of lovastatin, 10 ml (0.1 mol) of piperidine, 100 mg (0.82 mmol) of N,N-dimethylaminopyridine and 30 ml of toluene was refluxed for 36 hours. The mixture was cooled to RT and washed with 2x30 ml of 2 N HCl and 2x20 ml of water. The organic layer was dried with sodium sulfate, filtered and evaporated. The residue was stirred with hexane and the resulting precipitate was filtered to give 0.87 g of lovastatin piperidinamide as a white solid.

Example 2:

Reaction of lovastatin butylamide with thionylchloride:

0.76 G (7.5 mmol) of triethylamine was added to a solution of 1.2 g (2.5 mmol) of lovastatin butylamide in 20 ml of toluene. Surprisingly 0.45 g (3.7 mmol) of thionylchloride was added dropwise. After 1 hour at room temperature the reaction mixture was washed with water, dried (sodium sulphate), filtered and evaporated to give a brown oil.

Example 3

Reaction of lovastatin butylamide with phosphorylchloride:

0.76 G (7.5 mmol) of triethylamine was added to a solution of 1.2 g (2.5 mmol) of lovastatin butylamide in 20 ml toluene. Next 0.58 g (3.8 mmol) of phosphorylchloride was added dropwise. After 1h at room temperature the reaction mixture was filtered, dried (sodium sulphate), filtered and evaporated to give a brown oil.

Example 4:

Process for preparing simvastatin by direct methylation.

A. Formation of the acetonide of lovastatin butylamide, exemplified as formula II' in figure II:

A mixture of 40 g (98 mmol) of lovastatin and 60 ml of n-butylamine was refluxed for 1 hour, evaporated and coevaporated twice with 100 ml of toluene. The resulting crude amide was dissolved in 500 ml of acetone and 3 g of p-TsOH was added. The clear solution was stirred at room temperature (RT) for two hours at which time a solid was formed. The mixture was cooled to -10°C for three hours and the solid was collected and dried to afford 45 g (88%) of the amide/acetonide as a white solid. From the mother-liquor another 5 g was obtained, by partially evaporation of the solvent.

B. Alkylation of amide/acetonide intermediate formed in step A:

The amide/acetonide (19.5 g, 37.6 mmol) in 280 ml THF/cyclohexane (4/1) was cooled to -40°C and 113 ml 1M lithium-pyrrolide (prepared from pyrrolidine and n-butyllithium at -15°C) was added maintaining the temperature at <-30°C. The solution was stirred at -35°C for two hours and 5 ml MeI was added in one portion. The solution was stirred at -30°C for one hour and the temperature was allowed to rise to -10°C. 300 Ml of 1N HCl was added and the resulting mixture was refluxed for one hour. Ethyl acetate (300 ml) was added and the organic layer was washed with 100 ml of 3N HCl and evaporated.

300 Ml of methanol and 125 ml of 2N NaOH were added to the residue. The mixture was refluxed for 12 hours and most of the methanol was evaporated. 120 Ml of water and 300 ml of ethyl acetate were added and the pH was adjusted to 5 with 3N HCl. To the organic layer were added 60 ml of methanol and 25 ml of NH_4OH/methanol (1/3). The resulting mixture was stirred for one hour at room temperature and then cooled to 10°C. The solid was collected and dried. The yield was 13.5 g (80%) of simvastatin ammonium salt.

Example 5:

Process for the preparation of simvastatin from lovastatin by reduction of the R_3 ester moiety.

A. Formation of the acetonide of lovastatin butylamide:

A mixture of lovastatin (40.5 g, 100 mmol) and 75 ml of n-butylamine was heated at reflux for 1 hour. The excess of amine was evaporated and coevaporated with 100 ml of toluene. To the crude amide was added 400 ml of acetone and 5 g of p-TsOH. The mixture was stirred at RT for 1 hour and then cooled in ice/water for 2 hours. The resulting solid was collected by filtration and dried. From the mother-liquor a second batch was obtained. Total yield 49 g (94-95%).

B1. Reduction of the intermediate formed in step A with lithiumaluminiumhydride:

The compound as formed in step A (45 g, 87 mmol) was dissolved in 200 ml of THF and added dropwise to a suspension of 7 g (2,1 equivalents) of lithiumaluminiumhydride ($LiAlH_4$) in 100 ml of THF at 10-15°C in ca. 20 minutes. The mixture was stirred for 30 minutes. The reaction mixture was treated with a solution of 20% KOH (exothermic). The resulting salts were removed by filtration and washed with 200 ml of THF. The combined filtrates were evaporated to afford 35.5 g of a syrup.

B2. Reduction of the intermediate formed in step A with methylmagnesiumchloride (Grignard):

A solution of 2 g (3.9 mmol) of the compound as formed in step A, in 20 ml of THF was cooled to 0°C. A solution of 12 ml of 3M methylmagnesiumchloride was added dropwise in 20 minutes. After 18 hours at RT the lovastatin n-butylamide acetonide was converted completely.

B3. R duction of the intermediate formed in step A with n-butyllithium:

A solution of the compound as formed in step A (1 g, 1.9 mmol) in 25 ml THF was cooled to -50°C. A solution of 2.5 M n-

butyllithium (2.74 ml) was added dropwise over a period of 10 minutes. After 18 hours stirring at RT the alcohol intermediate was formed.

C. Acylation of the intermediate formed in step B and conversion to ammonium salt of simvastatin:

3 G of 4-dimethylaminopyridine in 300 ml of pyridine was added to a solution of 25 g (57 mmol) of the intermediate formed in step B and the mixture was heated to 50-55°C, preferably 50°C. 2,2-Dimethylbutyric acid chloride (50 ml) was added in one portion and the resulting mixture was stirred for 40 hours (HPLC-analysis showed complete conversion). To the reaction mixture 400 of ml water and 400 ml of ethylacetate (EtOAc) was added. The organic layer was subsequently washed twice with 10% $NaHCO_3$ (400 ml), with water (400 ml) and with a solution of 10% HCl (400 ml). The organic layer was evaporated and dissolved in 200 ml of THF, 200 ml water was added, followed by 10 g of p-TsOH. The mixture was refluxed for 2 hours. EtOAc (400 ml) was added, followed by 300 ml water. The organic layer was washed twice with 10% $NaHCO_3$ (400 ml) and evaporated. The residue was dissolved in 300 ml of MeOH and 170 ml of 2N NaOH was added. The resulting mixture was refluxed for 3 hours and cooled to RT. Most of the MeOH was evaporated and 120 ml of water was added. The pH was adjusted to pH=7 with 2N HCl and 300 ml of EtOAc was added. The pH was further adjusted to pH=4 and the layers were separated. To the organic layer was added 100 ml of EtOH, followed by 40 ml of NH_4OH/MeOH (1/3). The mixture was stirred at -10°C for 2 hours and the solid collected and washed with EtOAc and EtOH (cold). Yield 16 g (62%), HPLC-analysis gave 98,9% of the ammonium salt of simvastatin.

D. Conversion of the simvastatin ammonium salt to simvastatin:

A suspension of 9 g of the ammonium salt of simvastatin as formed in step C was heated in 250 ml of toluene at 100°C for 6 hours. The mixture was refluxed for an additional 30 minutes, filtered and evaporated. To the residue 100 ml of cyclohexane was added and the solution was evaporated again. The crude

simvastatin was recrystallised from ca. 150 ml of cyclohexane to afford simvastatin as a white solid. Yield 85%, HPLC-analysis gave 98,4% of simvastatin.

Example 6:

Process for the preparation of simvastatin from lovastatin by reduction of the R_3 ester moiety.

A: Preparation of the acetonide of lovastatin butyl amide.

A mixture of 950 g of lovastatin (2.4 mol), 8 l of toluene and 500 ml of n-butylamine (5 mol) is heated up to 85°C under nitrogen. The solution is kept at 85°C - 95°C during 2 hours, and is subsequently cooled to room temperature.

Then 5 l of 4 N sulfuric acid is added and the mixture is stirred during 5 minutes. The lower layer is removed, and 1.5 l (12 mol) of 2.2-dimethoxy propane are added to the upper layer. The solution is stirred during 30 minutes at room temperature, and thereafter the mixture is concentrated to 5.4 kg by evaporation at 55-60°C under vacuum.

B: Reduction of the intermediate formed in step A with lithium aluminium hydride

5.8 l (5.5 kg, corresponding to 2.4 mol of the intermediate obtained in step A) of the concentrate obtained in step A is mixed with 2 l of toluene. The mixture is cooled to 0°C under a nitrogen atmosphere. 6 L of a 1 N solution of Lithium aluminium hydride in toluene (6 mol $LiAlH_4$) is added over a period of 75 minutes, during which the temperature is kept below 8°C. The resulting mixture is stirred for 3 hours at 5-10°C, then 5.3 l of water over a period of 100 minutes, keeping the temperature below 10-15°C.

Subsequently, 5 l of 4 N sulfuric acid is added to the suspension and the mixture is stirred during 15 minutes. Hereafter, the layers are allowed to settle. The milky lower layer is removed, and the upper layer is washed with 4.5 l of water and with 6 l of an aqueous 1 N sodium hydroxide solution. 6 L of the upper layer a removed by evaporation at 50-60°C under vacuum (150-300 mm Hg).

C: Acylation of the intermediate obtained in step B with 2.2-dimethyl butyryl chloride

To the solution of the alcohol intermediate in toluene obtained in step B, containing 2.4 mol of intermediate, 250 ml of toluene containing 35 g (0.29 mol) of 4-(N,N-dimethyl amino)pyridine, 1.6 l of triethylamine (11.4 mol) and 1.5 kg (11 mol) of 2.2-dimethyl butyryl chloride are added. The resulting solution is heated to 105-110°C, and stirred at this temperature during 10 hours under nitrogen.

Hereafter, the resulting suspension is cooled to room temperature, and 3 l of 4 N sulfuric acid is added. The mixture is stirred for 5 minutes, and then the layers are allowed to separate. Subsequently the lower layer is removed, and the upper layer is washed with 2 l of 4 N sulfuric acid.

D: Preparation of simvastatin ammonium salt

The reaction mixture obtained in Step C (circa 11 l) is mixed with 4.5 l of 4 N sulfuric acid. The mixture is subsequently heated at 70-75°C during 3 hours, while nitrogen is led through the mixture. Then the mixture is allowed to cool to room temperature, and the lower layer is removed. The upper layer is cooled to 5°C and washed with 2.5 l of 2 N sodium hydroxide. After removal of the lower layer, 6 l of 2 N sulfuric acid is added and stirred during 3 hours at room temperature, and then at 45-55°C during 3 hours. The suspension is cooled to 5-10°C, whereafter 2.75 l of 4 N sulfuric acid is added while the temperature is kept below 10°C. Then the lower layer is removed, and 1 l of a concentrated NH_4OH solution is added. Subsequently, the mixture is concentrated at 50-60°C under vacuum in order to remove toluene and water. 3 l of ethyl acetate is added to the residue, and the mixture is stirred at 50°C during 30 minutes to obtain a homogeneous suspension. The suspension is cooled to room temperature and filtered under vacuum. The filter cake is subsequently washed with 1 l of ethyl acetate and subsequently it is suspended in 4 l of ethyl acetate, heated at 50°C for 90 minutes, the warm suspension is filtrated and the filter cake

is washed in ethyl acetate, yielding 891 g of crystals of simvastatin ammonium salt.

E: Preparation of simvastatin

570 g of the ammonium salt crystals as obtained in step D are suspended in 13 l of toluene. Subsequently 2 l of water is added, and the pH is adjusted to 3 by addition of 4 N sulfuric acid. The mixture is stirred during 30 minutes, whereafter the lower layer is removed. The upper layer is subsequently washed with 2 l of water, and concentrated by evaporation of 4 l of toluene at 50-60°C under vacuum.

The remaining solution is heated at 85-92°C under nitrogen during 2.5 hours. Then, the solution is cooled to 15°C, 3 l of water is added and the pH is adjusted to pH 8-8.5 by addition of a solution of 1 N NaOH. The lower layer is removed and 3 l of water is added to the upper layer followed by adjustment of the pH to 6 by adding 6N sulfuric acid.

The lower layer is removed, and the upper layer is concentrated to 1 l by evaporation at 50-60°C under vacuum.

Subsequently 350 ml of n-hexane is added over a period of 1 hour at 50-60°C. Subsequently the mixture is stirred at 50-60°C during 30 minutes and then slowly cooled to 15°C over a period of 2 hours. The crystals are filtered and washed with 350 ml of a mixture of n-hexane/toluene (5/1), yielding 440 g of simvastatin.

Example 7:

Process for the preparation of simvastatin ammonium salt by reduction of the R_1 ester moiety of lovastatin.

A. Formation of lovastatin cyclohexanamide:

A mixture of 5 g (0.012 mol) of lovastatin, 6 ml (0.052 mol) of cyclohexylamine and 50 ml of toluene was refluxed for 6 hours. The reaction mixture was cooled to RT and 20 ml of ethylacetate was added. The mixture was washed with 2N HCl (2 x 30ml) and water (2 x 20ml). The organic layer was dried with sodium sulfate, filtered and evaporated to a volume of 15 ml. 50 Ml of

hexane was added and the precipitate was filtered to give 5.5 g of lovastatin cyclohexanamide as a white powder.

B. Formation of lovastatin cyclohexanamide acetonide:

To a solution of 5 g (10 mmol) of lovastatin cyclohexanamide in 25 ml of acetone was added 300 mg (1.6 mmol) of p-TsOH. After 18 hours stirring at RT the solution was poured into a mixture of 50 ml ethylacetate and 50 ml, 10% sodium bicarbonate solution. The ethylacetate layer was separated, washed with 30 ml, 10% sodium bicarbonate solution, dried with sodium sulfate, filtered and evaporated. The residue was dissolved in toluene and which was subsequently evaporated to give 4.9 g of the acetonide of lovastatin cyclohexanamide.

C. Formation of simvastatin ammonium salt:

A suspension of 836 mg (22 mmol) of lithiumaluminiumhydride in 15 ml of THF was cooled to 0°C and a solution of 4.93 g (9.1 mmol) of the compound formed in step B, in 20 ml of THF was added dropwise over a period of 15 minutes. After 18 hours at RT the reaction mixture was cooled at 0°C and 1 ml of water and of a 10% potassium hydroxide solution were added subsequently. The mixture was filtered over Celite and the THF was evaporated to give the corresponding 4.3 g (9 mmol) of alcohol intermediate.

D. Formation of simvastatin ammonium salt:

A mixture of 4.3 g (9 mmol) of the alcohol intermediate, 40 ml of pyridine, 200 mg N,N-dimethylaminopyridine and 7.2 g, (54 mmol) of 2,2-dimethylbutyric acid chloride was stirred for 72 hours at 65°C. The mixture was cooled, 100 ml of toluene was added and the mixture was washed with 2x50 ml of a 10% sodium bicarbonate solution and 30 ml of brine. The toluene layer was dried with sodium sulfate, filtered and evaporated. The residue was dissolved in 100 ml of toluene, which was subsequently evaporated.

The residue was dissolved in 20 ml of THF and 20 ml of water. Next 1 g of p-TsOH was added and the solution was refluxed for

5 hours. The solution was poured into a mixture of 70 ml of toluene and 50 ml of 10% sodium bicarbonate solution. The organic layer was separated and washed with 30 ml of 10% sodium bicarbonate solution. The organic layer was dried, filtered and evaporated to give 4,8 g residue.
The residue was dissolved in 70 ml of methanol and 40 ml of 2M NaOH. The reaction mixture was refluxed for 72 hours. The methanol was evaporated and the water layer was cooled to 0°C. The water layer was acidified to pH = 5 with a 2N HCl solution. Next 75 ml of ethylacetate was added and the organic layer was separated. To the ethylacetate was added 5 ml 25% of ammonia solution. The precipitate was filtered to give 1.1 g of the ammonium salt of simvastatin, with an overall yield of 27% from the acetonide of lovastatin cyclohexanamide.

Example 8:

Preparation of diacylated simvastatin butylamide:

A. Silylation of lovastatin butylamide

T-butyl dimethylsilyl lovastatinbutylamide was prepared by literature procedure (Askin D; Verhoeven, T.R.; Liu, T,M.-H.; Shinkai, I. *J.Org.Chem,* **1991**, 56, 4929) and obtained with a yield of 68% (crude material), HPLC R_f: 12.87.

B. Reduction of t-butyl dimethylsilyl lovastatin butylamide

A solution of t-butyl dimethylsilyl lovastatin butylamide (1,65 g, 2.34 mmol) in THF (30ml) was added to a 1M solution of $LiAlH_4$.2THF in toluene (6ml, 2.5 eq,) at 0°C. The reaction mixture was stirred for 2h, after which moist sodium sulfate ($Na_2SO_4.nH_2O$) was added until gas evolution ceased. Attempts to filter the slurry over a glass funnel (P2) with Celite layer failed. The reaction mixture was poured in dilute HCl (<1N). The water layer was extracted with diethylether. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. Yield: 1.07 g (89%).
HPLC: R_f:9.27.

C. Acylation of t-butyl silyl protected lovastatin butylamide alcohol

To a solution of the alcohol intermediate obtained in step 8B (360 mg, 0.58 mmol) and triethylamine (0.32 ml) in toluene (10 ml), 2,2-dimethylbutyryl chloride was added.

(0.31 g, 4 eq.). The reaction mixture was heated to reflux for 10h (standard procedure). HPLC analysis showed a mixture of compounds among which the desired diacylated product (R_r:15,81). Removal of the protecting groups according to the method described in Askin D; Verhoeven, T.R.; Liu, T,M.-H.; Shinkai, I. *J.Org.Chem*, **1991**, 56, 4929) and obtained with a yield of 68% (crude material), HPLC R_f: 12.87.

Example 9:

Preparation of the diacetylbenzylidene derivative of lovastatin:

A) Formation of the benzylidene derivative of lovastatin butylamide

The lovastatin butylamide (4.77 g, 10 mmol) was dissolved in toluene (50 ml). Thereafter, benzaldehyde (10.6 g, 10 eq) and p-TsOH (500 mg) were added and stirred during 16 hours at room temperature. A saturated aqueous solution of $NaHCO_3$ was added and the layers were separated. The toluene layer was washed with saturated $NaHCO_3$ (aq), saturated NaCl (aq), dried (Na_2SO_4) and evaporated. The residue was purified further by applying column chromatography (SiO_2)/n-Hexane/ethylacetate, which yielded 2.6 g (46%) of the endproduct.

B) Reduction of the benzylidene derivative

The benzylidene derivative (2.6 g, 4.6 mmol) was dissolved in toluene (50 ml) and the solution was cooled to 0°C. Then a solution of 1M LiAlH.2THF (11.5 ml) in toluene was added dropwise while the temperature was kept under 10°C. Then the solution was stirred for 2 hours at 0-5°C. Hereafter 30% NaOH (aq, 1.8 ml) was added and the mixture was stirred for 16 hours at room temperature. The mixture was filtered over Celite, washed with toluene (50 ml) and concentrated to about 50 ml.

C) Formation of the benzylidene derivative of simvastatin

Triethylamine (1.9 g, 4.1 eq), dimethylbutyric acid (2.5 g, 4 eq) and dimethylaminopyridine (50 mg) were added to the reaction mixture formed in step 9B and refluxed during 16 hours. The mixture was then poured into water/ethylacetate and separated.

The organic layer was subsequently washed with water, followed by saturated sodium chloride, then dried with sodium sulfate and evaporated, yielding 3.3 g of crude product.

Further conversion of the product to simvastatin to be carried out according to the procedure described in Example 5C and 5D, second part.

Example 10:

Lovastatin reduction of the acetonide of lovastatin pyrrolidin amide:

40 Mg (1.1 mmol) of lithiumaluminiumhydride was added at 0°C to a solution of 1 g (1.94 mmol) of the acetonide of lovastatine pyrolidin butylamide (prepared analogous to the method described in example 3 by reaction of lovastatin and pyrrolidin) in 20 ml THF. After 18 hours at room temperature the conversion was 50%.

Example 11

Reduction of lovastatin butylamide:

To a suspension of $LiALH_4$ (400 mg 10.5 mmol) in THF (50 ml) was added a solution of lovastatin butylamide (2.25 g, 5 mmol) in THF (25 ml) at 0°C. The mixture was stirred for 16 h at ambient temperature. Moist sodium sulfate ($Na_2SO_4.n2H_2O$, Glauber salt analogue) was added until gas evolution ceased after which dry Na_2SO_4 was added. The slurry was filtered over a glass filter and the filtrate was evaporated under reduced pressure to dryness to give a thick brouwn oil (1.03 g, 53%) HPLC of the crude material; R_1; 2.93 (and 5.79, starting material).

Example 12:

Selective acylation reaction on the nitrogen of the lovastatin butylamide acetonide alcohol, whereafter the OH group can be acylated:

To a solution of lovastatin butylamamide acetonide alcohol (2.1 g, 5 mmol) and triethylamine (0.8 ml, 5.5 mmol) in toluene (50 ml) was added 1.1 eq. benzoyl chloride (0.64 ml, 5.5 mmol) at 0°C. The reaction mixture was stirred for 16h at room temperature. A HPLC sample displayed major peaks at R_f 6.16 (starting material) and 9.13. After 21 h a peak at 9.67 was coming up. NMR analysis showed a small NH peak and 3 other peaks in the regio 6,5-5 ppm, indicating that the amide is acylated.

Example 13:

Reaction of lovastatin with ammonia

A suspension of 0.25 g (0.6 mmol) lovastatin in 15 ml of methanol was cooled to 5°C on an ice/water bath. The methanol was saturated with ammonia (gas) and the mixture was heated for 40 hours at 130°C in a sealed tube. The reaction mixture contained 43% of the corresponding deacylated product according to HPLC-analysis.

Example 14:

Reaction of lovastatin with n-butylamine

A solution of 0.5 g (1.2 mmol) of lovastatin in 15 ml of n-butylamine was heated for 40 hours at 150°C in a sealed vessel. The reaction mixture contained 12.3% of the corresponding deacylated product according to HPLC analysis. The structure of the deacylated butylamide was confirmed by forming the corresponding acetonide by reaction with pTsOH and acetone and comparing the acetonide with another sample of acetonide made by the process described in the second part of example 5A.

Example 15:

Reaction of lovastatin with n-heptylamine

A solution of 0.25 g (1.2 mmol) of lovastatin in 10 ml of heptylamine was refluxed for 70 hours. The resulting reaction mixture contained 17% of the corresponding deacylated product according to HPLC analysis.

Example 16:

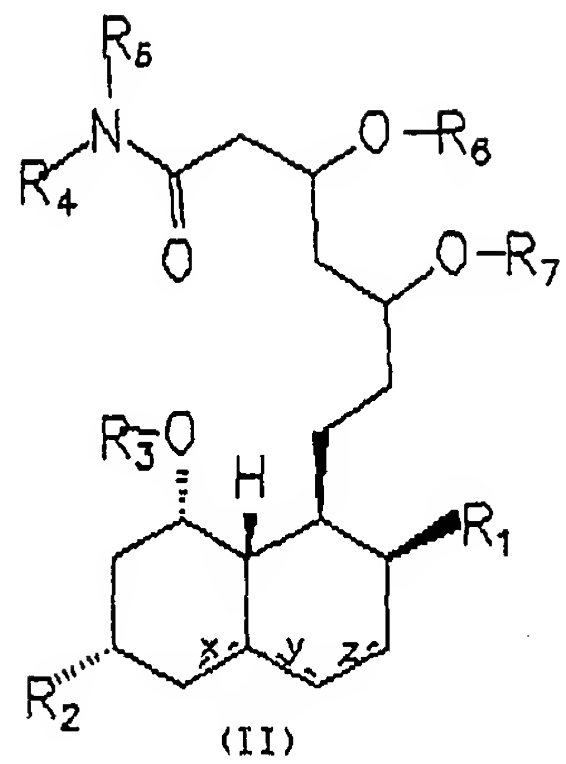
All three deacylated compounds from Examples 13, 14 and 15 were converted into the corresponding acetonide (i.e. by ring closure) by addition of 400 ml of acetone and 5 g of p-TsOH. The mixture was stirred for 1 hour (at room temperature) and then cooled in ice water for 2 hours. The resulting solid was collected by suction and dried.

Example 17:

The three acetonide compounds resulting from Example 16 were then each individually converted to simvastatin using the acylation and ammonium salt conversion reactions as described in steps C and D of Example 5.

CLAIMS

1. A compound of formula II,



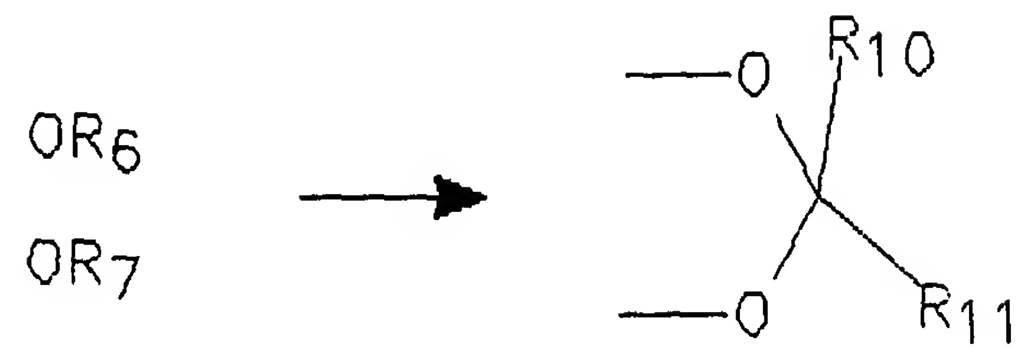
(II)

wherein R_1 and R_2 are independently selected from the group consisting essentially of a hydrogen atom, a hydroxyl, C_{1-10}alkyl and C_{6-14}aryl and C_{6-14}arylC_{1-3}alkyl,
and wherein R_3 is R_9-C=O or hydrogen,
and wherein each of R_9, R_4 and R_5 are independently selected from the group comprising:

(1) C_{1-15} alkyl, straight or branched,
(2) C_{3-15}cycloalkyl,
(3) C_{2-15}alkenyl, straight or branched,
(4) C_{2-15}alkynyl, straight or branched,
(5) phenyl
(6) phenylC_{1-6}alkyl-

and R_9 may also be each of the definitions mentioned under (1) to (6) substituted with one or more of the substituents independently selected from the group comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy and C_{6-14}aryl,
and R_4 and R_5 may also be hydrogen or form with the nitrogen to which they are attached, a 5, 6 or 7 membered heterocycle moiety such as a pyrrolidine, piperidine or a homopiperidine,
and wherein R_6 and R_7 are also independently selected from the group which form:

(1) a dioxane moiety,



wherein R_{10} and R_{11} are independently selected from the group comprising:

(1) C_{1-15} alkyl, straight or branched,

(2) C_{3-15}cycloalkyl,

(3) C_{2-15}alkenyl, straight or branched,

(4) C_{2-15}alkynyl, straight or branched,

(5) phenyl,

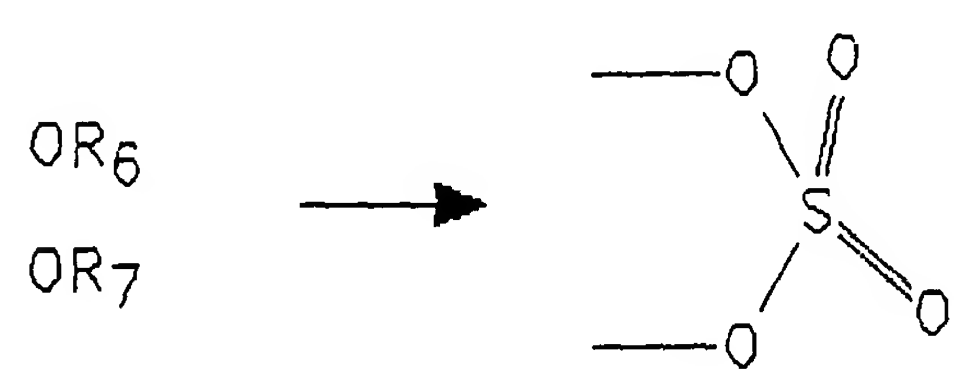
(6) phenylC_{1-6}alkyl-,

all optionally substituted with one or more of the substituents independently selected from the group comprising halogen C_{1-6}alkyl, C_{1-6}alkoxy or C_{6-14}aryl.

(7) hydrogen, with the proviso that R_{10} is not hydrogen,

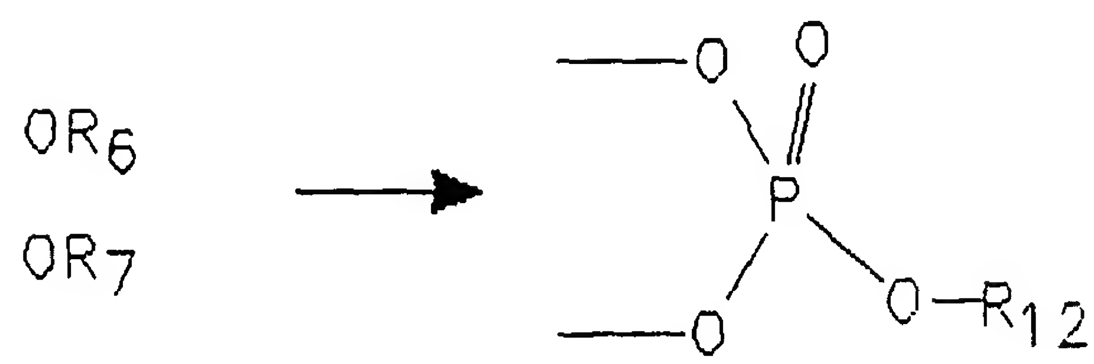
(8) R_{10} and R_{11} are forming an optionally substituted 5, 6, 7 or 8 membered cyclic moiety, in which one or more of the substituents are selected from the group comprising halogen and a lower alkyl in any combination,

(2) a cyclic sulfate,



(3) or a cyclic phosphate,

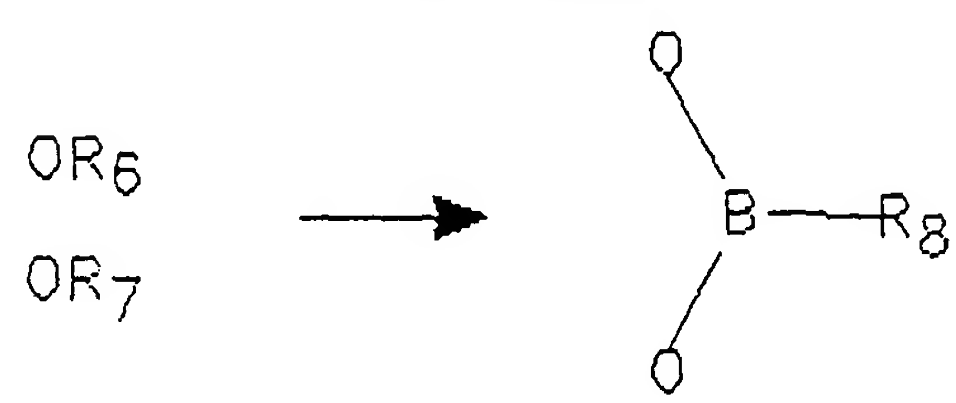
in which R_{12} is selected from the group comprising:



(1) C_{1-15} alkyl, straight or branched,
(2) C_{3-15}cycloalkyl,
(3) phenyl,
(4) phenylC_{1-6}alkyl-,
(5) hydrogen,
(6) primary amines, preferably n-butylamine and cyclohexylamine or secondary amines,

and with the proviso that when R_3 is hydrogen, R_6 and R_7 may also form a

(1) borylidene group,

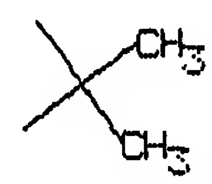


in which R_8 is a phenyl optionally substituted by one to five substituents, halogen or lower alkyl in any combination, preferably phenyl or para fluoro phenyl, or

(2) R_6 and R_7 are both hydrogen,

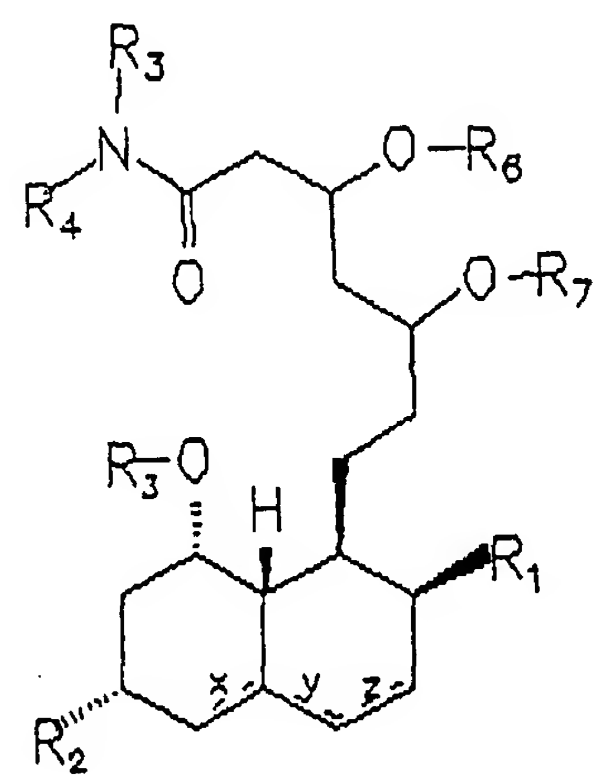
and wherein the dotted lines at x, y and z represent possible double bonds, when any are present, being either x and z in combination or x, y or z alone or none; or a corresponding stereoisomer thereof.

2. A compound according to claim 1, wherein independently R_1 is methyl, R_2 is methyl, R_3 is 2-methylbutyrate, R_4 is n-butyl, R_5 is selected from the group consisting of hydrogen, 1-methylpropyl or 1,1-dimethylpropyl, R6 and R7 form together



R_8 is phenyl or parafluoro phenyl and x and z are double bonds.

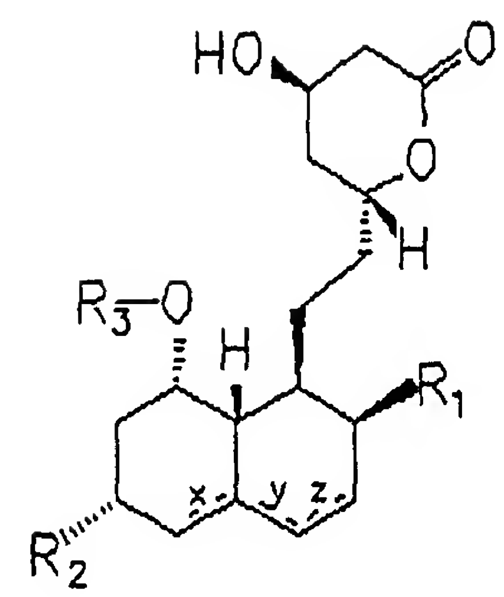
3. A compound of formula IV,



(IV)

wherein R_1, R_2, R_3, R_4, R_6 and R_7 and x, y and z are defined as for a compound of formula II in Claim 1, or a corresponding stereoisomer thereof,
with the proviso that R_3 and R_4 are not hydrogen, and R_6 and R_7 may also form a borylidene group, as defined in Claim 1.

4. A process for the preparation of a compound of formula II as defined in Claim 1 comprising reacting a compound of formula I,



(I)

wherein R_1, R_2 and R_3 and x, y and z are defined as for a compound of formula II in Claim 1, with the proviso that R_3 is not hydrogen and R_1, R_2, x, y and z are the same for the starting material and the endproduct, or a corresponding stereoisomer thereof,
with a corresponding amine, followed by the protection of the hydroxyl of the former lactone ring, by reaction with a protective group forming agent, optionally in the presence of one or more suitable catalytic agents.

5. A process according to claim 4 for the preparation of a compound of formula II with R_3 is 2-methylbutyrate from a compound of formula I with R_3 is 2-methylbutylrate.

6. The process according to Claim 4 or 5, wherein the amines are selected from the group comprising:

(1) ammonia,
(2) primary amines, and,
(3) secondary amines,

and the protective group forming agents are selected from the group comprising:

(1) ketones, preferably acetone,
(2) aldehydes,
(3) acetals,
(4) sulfonyl chloride, followed by oxidation with sodium periodate,

(5) phosphonyl chloride, followed by reaction with an alcohol, amine or water,

(6) boronic acid,

and the catalytic agents are selected from the group comprising:

(1) para-toluene sulphonic acid,

(2) sulfuric acid.

7. A process for the preparation of a compound of formula II as defined in Claim 1, with the proviso that R_3 is hydrogen, and wherein both R_6 and R_7 may also be hydrogen or a silyl protecting group as for instance t-butyl dimethyl silyl, comprising reacting a compound of formula II as defined in Claim 1, with the proviso that R_3 is not hydrogen, and wherein both R_6 and R_7 may also be hydrogen or a silyl protecting group as for instance t-butyl dimethyl silyl or form a borylidene moiety, and where all the parameters R, x, y and z are the same for the starting material and the endproduct except for R_3,
with suitable reducing agents to reduce the R_3 ester moiety.

8. The process according to Claim 7 wherein the reducing agents are selected from the group comprising:

(1) lithiumaluminiumhydride,

(2) aluminiumhydride,

(3) diisobutylaluminiumhydride,

(4) LiY and wherein Y is C_{1-6}alkyl or C_{6-14}aryl, preferably Y is n-butyl, and

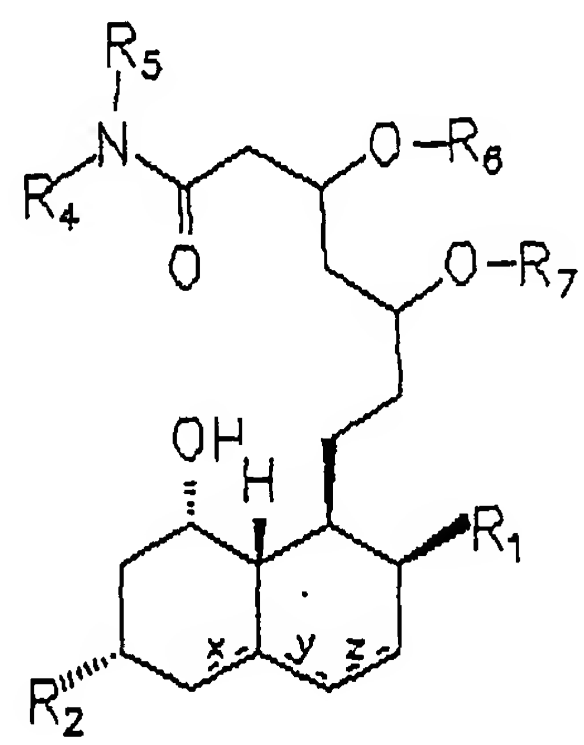
(5) ZMgCl, ZMgBr wherein Z is C_{1-6}alkyl or C_{6-14}aryl, preferably Z is methyl.

9. A process for the preparation of a compound of formula II as defined in Claim 1, with the proviso that R_3 is hydrogen, and wherein both R_6 and R_7 may also be hydrogen or a silyl protecting group as for instance t-butyl dimethyl silyl, comprising reacting a compound of formula II as defined in Claim 1, with the proviso that R_3 is not hydrogen, and wherein both R_6 and R_7 may also be hydrogen or a silyl protecting group as for instance

t-butyl dimethyl silyl or form a borylidene moiety, and where all the parameters R, x, y and z are the same for the starting material and the endproduct except for R_3 with a primary amine of the formula R_4NH_2 with R_4 as defined in claim 1, with the proviso that R_4 is not part of a heterocycle moiety.

10. A process for the preparation of a compound of formula II as defined in claim 1, with the proviso that R_3, R_5, R_6 and R_7 are hydrogen, and R_1, R_2, x, y and z are the same for the starting material and the endproduct, comprising reacting a compound of formula I as defined in claim 4, with an excess of a primary amine of the formula R_4NH_2 as defined in claim 9 at a temperature between about 100°C and 250°C.

11. A process for the preparation of a compound of formula IV as defined in Claim 3, comprising reacting a compound of formula III, or the corresponding stereo isomer thereof,



(III)

wherein R_1, R_2, R_4, R_6 and R_7 are defined as formula II in Claim 5, and R_5 is hydrogen, and with the proviso that R_6 and R_7 are not hydrogen, and were all the parameters R, x, y and z are the same for the starting material and the endproduct, with a suitable corresponding acylation agent.

12. A process for the preparation of a compound of formula II as defined in Claim 1, with the proviso that R_3, R_5, R_6, R_7 are not hydrogen, comprising reacting a compound of formula II wherein R_1, R_2, R_4, R_5, R_6 and R_7 are as defined in Claim 1 and R_3 is hydrogen, with the proviso that R_5, R_6 and R_7 are not hydrogen, and were all the parameters R, x, y and z are the same the for starting material and the endproduct except for R_3, with a suitable corresponding acylation agent.

13. The process according to Claim 8 and 9 wherein the acylation agents are selected from the group comprising:

(1) acid chloride of the corresponding acyl group,

(2) free acid of the corresponding acyl group.

(3) acid anhydride of the corresponding acyl group.

14. A process to obtain a compound of formula I as defined in Claim 4, from formula I as defined in Claim 4, with the proviso that the R_3 moiety of the compound as prepared may be different from the R_3 moiety of the starting compound and where the other parameters are further the same for starting material and endproduct, comprising the following steps:

a) ring opening of the lactone by formation of an amide bond and forming a protective group according to Claim 4,

b) reduction of the R_3 moiety of formula II according to Claim 7,

c) acylation of the compound of formula III according to Claim 11 or a compound of formula II according to Claim 12,

d) removal of the acetal moiety and hydrolysis of the amide group of formula IV as defined in Claim 3, or of a compound of formula II as defined in Claim 1, into formula V, wherein M forms any pharmaceutically acceptable salt, acid or ester,

e) lactonization of formula V into formula I by heating.

15. A process to obtain a compound of formula I as defined in Claim 4, from formula I as defined in Claim 4, with the proviso that the R_3 moiety of the compound as prepared may be different

from the R_3 moiety of the starting compound and where the other parameters are further the same for starting material and endproduct, comprising the following steps:

a) reacting the compound of formula I with an amine R_4NH_2 as defined in claim 9,

b) formation of a protective group according to claim 4,

c) acylation of the compound of formula III according to Claim 11 or a compound of formula II according to Claim 12,

d) removal of the acetal moiety and hydrolysis of the amide group of formula IV as defined in Claim 3, or of a compound of formula II as defined in Claim 1, into formula V, wherein M forms any pharmaceutically acceptable salt, acid or ester,

e) lactonization of formula V into formula I by heating.

16 . A process to prepare simvastatin from lovastatin according to Claim 12, characterized by the following steps:

a) ring opening of the lactone of lovastatin by formation of an amide bond with n-butylamine, followed by dioxane forming with acetone or dimethoxypropane,

b) reduction of the 2-methylbutyrate side chain of the compound formed in step a) by reaction with anyone of the reducing agents as defined in Claim 8,

c) acylation of the compound formed in step b) by reaction with 2,2-dimethylbutyl chloride in the presence of para-toluene sulphonic acid, hydrogen chloride or sulfuric acid.

d) removal of the dioxane moiety and of the amide group of the compound formed in step c) by hydrolysis, optionally followed by reaction with ammonium hydroxide to form ammonium salt of simvastatin,

e) lactonization of the ammonium salt or sodium salt of simvastatin or by heating in toluene to form simvastatin, followed by crystallization.

17. A process to prepare simvastatin from lovastatin, comprising the following steps:

a) ring opening of the lactone of lovastatin by formation of an amide bond with n-butylamine, followed by dioxane forming with acetone or dimethoxypropane,

b) α-methylation of the 2-methylbutyrate side chain of the compound formed in step a) with methyl iodide,

c) removal of the dioxane moiety and of the amide group of the compound formed in step a) by hydrolysis, optionally followed by reaction with ammonium hydroxide to form ammonium salt of simvastatin,

d) lactonization of the ammonium salt or sodium salt of simvastatin or by heating in toluene to form simvastatin, followed by crystallization.

18. A process for preparing simvastatin according to Claim 16 or 17 from a crude lovastatin, which may contain upto about 30% of impurities, such as dihydrolovastatin or oxidized lovastatin.

Figure 1

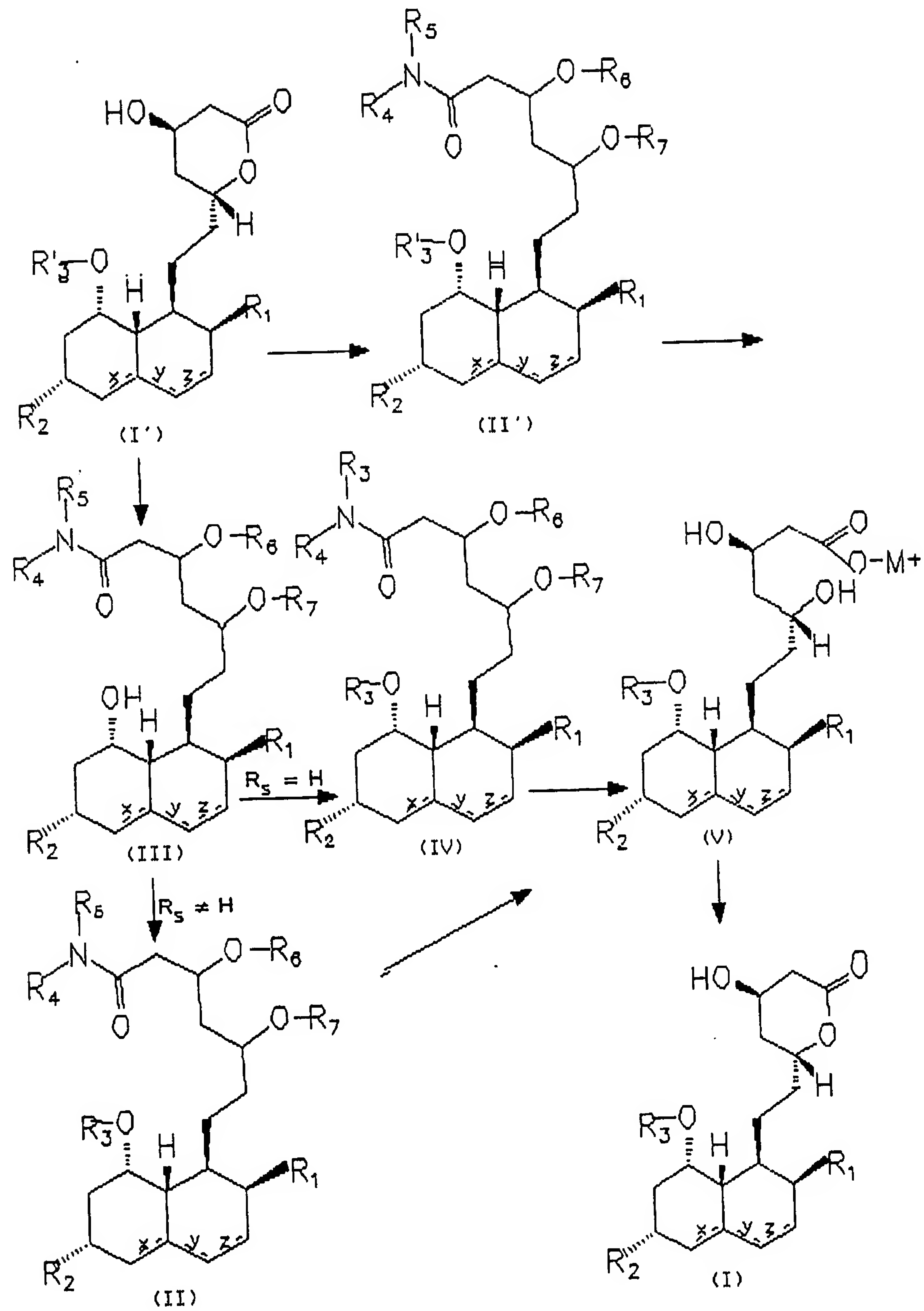
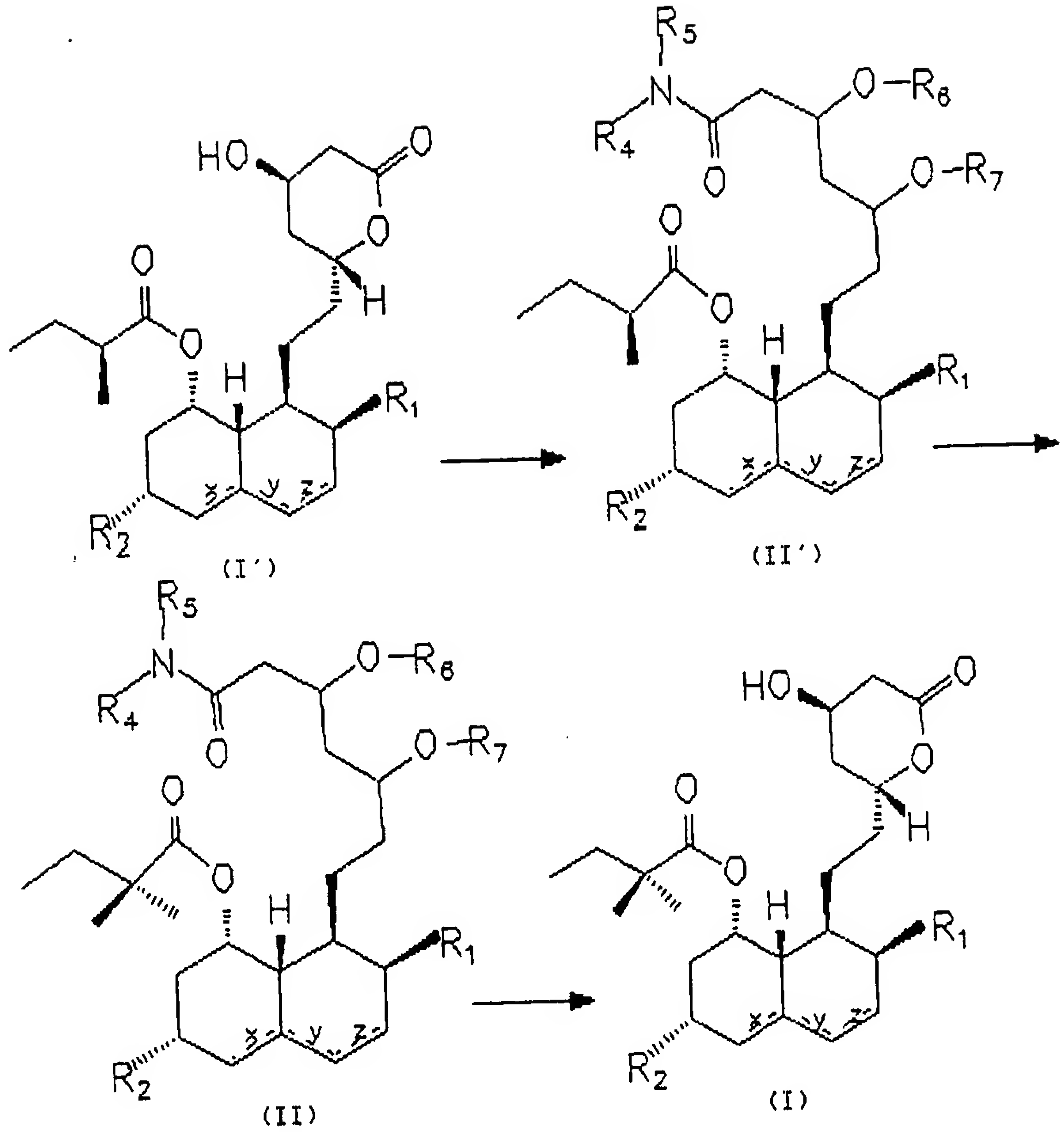


Figure 2



INTERNATIONAL SEARCH REPORT

Inte. ..onal Application No
PCT/EP 98/00519

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D309/30 C07C235/26 C07C235/30 C07D319/06 C07D327/10
C07F9/6574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 13283 A (APOTEX INC) 18 May 1995 cited in the application see claims ---	1-18
A	ASKIN D ET AL: "SYNTHESIS OF SYNVINOLIN: EXTREMELY HIGH CONVERSION ALKYLATION OF AN ESTER ENOLATE" JOURNAL OF ORGANIC CHEMISTRY, vol. 56, no. 16, 2 August 1991, pages 4929-4932, XP000676448 ---	1-18
A	EP 0 415 488 A (MERCK & CO INC) 6 March 1991 see claims --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 April 1998	04/05/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/00519

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 299 656 A (MERCK & CO INC) 18 January 1989 cited in the application see page 1 - page 10 -----	1-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte: onal Application No
PCT/EP 98/00519

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513283 A	18-05-1995	US 5393893 A	28-02-1995
		AU 8055594 A	29-05-1995
		CA 2173830 A	18-05-1995
		ZA 9408775 A	10-07-1995
EP 0415488 A	06-03-1991	CA 2024248 A	01-03-1991
		DE 69008277 D	26-05-1994
		JP 3184940 A	12-08-1991
		US 5098931 A	24-03-1992
EP 0299656 A	18-01-1989	US 4820850 A	11-04-1989
		AU 604937 B	03-01-1991
		CA 1287063 A	30-07-1991
		CN 1031086 A,B	15-02-1989
		CY 1613 A	10-07-1992
		DK 380788 A	15-02-1989
		FI 883184 A,B,	11-01-1989
		HK 98991 A	13-12-1991
		IE 61025 B	07-09-1994
		JP 1070481 A	15-03-1989
		JP 1988037 C	08-11-1995
		JP 7017663 B	01-03-1995
		JP 2527535 B	28-08-1996
		JP 7196641 A	01-08-1995
		KR 9509314 B	19-08-1995
		PT 87909 A,B	30-06-1989
		ZA 8804924 A	17-01-1989